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Links Between Pain Sensitivity and Alcohol Dependence

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Links Between Pain Sensitivity and Alcohol Dependence

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Abstract

Scientists have long wondered why some individuals are more sensitive to pain than others. While individual differences in pain have traditionally been discounted due to neuroticism, research has shown that individuals who are more sensitive to pain demonstrate real biological differences in pain perception (Coghill, McHaffie & Yen, 2003). However, individual differences in pain sensitivity remain under-explored in research and clinical settings that can provide further insights into clinical disorders such as addiction. The current research review is interested in examining the link between pain sensitivity and alcohol dependence. Investigating the relationship between pain sensitivity and alcohol addiction prompts many important peripheral questions such as whether increased pain sensitivity can serve as a useful biomarker for alcohol addiction, and how addiction to alcohol can cause changes in sensitivity to pain. Addiction potential or risk for addiction is a research area that is extremely important given that the high rate of addiction in this country is alarmingly high. The literature is sparse on the relationship between hyperalgesia or pain sensitization and risk for alcohol addiction. This literature review synthesizes current relevant research on pain and addiction, as well as addressing possible links between them.

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Introduction

Is there a link between pain sensitivity and alcohol addiction? People have often wondered why some individuals are more sensitive to pain and often complain about it, while others are impervious to everyday simple pains. As high rates of addiction continue to loom, the current scientific inquiry centers on relapse prevention. This innovative report explores the current literature on pain sensitivity, alcohol addiction, and the links they share, and is the first examination of its kind. While there have been a few studies on pain in patients with alcoholism, there is a deficit in the current literature as to whether greater initial individual sensitivity to pain may be a precursor for addiction. While the answer to this question is beyond the scope of this report, it is hoped that interest in this area will be stimulated. The present master's report is organized into three sections. In the first section, individual differences in pain perception are reviewed. The second section provides a short overview of alcoholism and vulnerabilities for developing alcohol dependence. The third and final section is focused on the links between them including shared neurobiological processes.

Chapter One:

Pain Sensitivity

Scientists have long wondered why some individuals are more sensitive to pain than others. Chapman and Jones (1944) conducted early research in the field of individual differences in pain perception. They interpreted their findings by categorizing the perception of pain as a sensory phenomenon, and the reaction to pain as a psychological phenomenon that may have vast clinical importance. Pain perception was defined as the subjective end-point by which participants first noticed the stimulus to be painful, and defined pain reaction as evidence of subjects' objective withdrawal from the pain stimulus. They found that both pain perception and pain reaction decreased with increasing age, and that while there was a small amount of variation within the individual, there was substantial variation between individuals to both pain perception and pain reaction (Chapman & Jones, 1943).

An individual's perception of pain is affected by a combination of the individual's emotions, damage to the body, genetics, and their expectations of pain (Hampton, 2006). In a review on pain, Coghill (2010) argued that while individuals' subjective experiences to sensory phenomena remain unique, differences between individuals' sensory experiences are derived from past experiences, the present environment, and future expectations. Additional research has shown that individuals who are more sensitive to pain demonstrate true differences in nociceptive processing (Coghill, McHaffie & Yen, 2003). Pain sensitivity is affected by three sets of factors that interact in complicated and multifaceted ways. Biological factors such as brain differences, sociocultural factors such

as gender roles, ethnicity, etc., genetics, and psychological factors such as mental illness, all mediate an individual's sensitivity to pain (Wiesenfeld-Hallin,, 2005).

Brain Differences in Pain Sensitivity

Although previously assumed ~~a~~ to be a passive and fixed relay system, pain perception is now understood to function as an active and complicated integrated system that is contingent upon the interactions of inhibitory and excitatory neurons (McGrath, 1994). Due to the high variability between individuals in subjective pain intensity, medical professionals have often wondered whether these differences are real or whether pain sensitive individuals are histrionic or drug seekers (Coghill, 2010). However, the between subject differences in brain regions that respond to pain have been shown to be consistent with inter-individual variability in pain intensity ratings, which provide support that individual differences in pain are genuine (Coghill, 2010). In an earlier study, Coghill and colleagues found within-individual differences in brain activation in the primary somatosensory cortex and anterior cingulate, in that activation increased in magnitude relative to pain stimulus intensity or its perceived intensity, which provided further support for the validity of individual variability in pain (Coghill, Sang, Maisog & Iadarola, 1999).

Coghill, McHaffie, and Yen (2003) conducted a functional neuroimaging study examining the neural correlates of thermal pain in normal control participants grouped as either low or high pain sensitive after subjectively rating their pain intensity. They found that when compared to low pain sensitive individuals, high pain sensitive individuals

displayed significantly increased activation in the anterior cingulate cortex, prefrontal cortex, and areas of the somatosensory cortex, which corresponded to areas where the pain stimulus was emitted (Coghill, McHaffie & Yen, 2003). Interestingly, the thalamus, a primary relay for nociceptive information, was similarly activated in both groups, suggesting that psychological factors may have contributed to the differences in pain perception (Coghill, McHaffie & Yen, 2003). For example, the thoughts and how much attention individuals devote to pain stimuli explain a portion of individual differences in pain perception (Coghill, 2010). The authors found that how focused an individual is on their thoughts and what thoughts they are currently experiencing both contribute to the subject's inter-individual differences in pain response (Coghill, 2010). For example, when participants divided attention between two noxious stimuli simultaneously delivered, they experienced reduced pain or even analgesia (Quevedo & Coghill, 2007).

Sex and Gender Differences in Pain Perception

In a consensus report among pain researchers, Greenspan and colleagues (2007) recommend that both sex and gender be used as constructs when examining group differences in pain report between men and women. As there are psychological differences between men and women, particularly in their response to stress, and since pain is a stressful experience in itself, Greenspan and colleagues (2007) assert that sex differences arising from stress influence observed gender differences found in pain studies.

According to Fillingim (2000), because women are overrepresented in a number of chronic pain conditions, and they report increased frequency of pain symptoms, they are at increased risk for developing pain conditions. Although women's higher pain sensitivity has been customarily attributed to sociocultural factors, such that feminine gender roles allow for the expression on pain, whereas male gender roles discourage such expression (Fillingim, 2000), sex differences in pain perception have been found in both human and non-human animals. Moreover, Fillingim (2000) forewarns researchers that different levels of analysis used for sex and gender may actually describe the same underlying processes.

Wiesenfeld-Hallin (2005) conducted a literature review of pain studies examining sex differences in humans and laboratory animals. Dispersed widely in the central nervous system, sex hormones influence sensitivity to pain. Thus, pain sensitivity in women varies with the menstrual cycle, with increased tolerance during the follicular phase rather than the luteal phase, as well as during late pregnancy (Wiesenfeld-Hallin, 2005). Women are also more regularly afflicted with chronic pain starting in puberty until 65 years of age (Berkley, 1997; Le Resche, Manci, Drangsholt, Saunders Korff, 2005; Von Korff, Dworkin, Le Resche, & Kruger, 1988). This finding may be confounded by the increased rate of depression and anxiety in women, which are associated with increases in pain symptoms. For instance, women with chronic pain exhibit greater rates of catastrophizing, which is linked to higher pain levels (Keogh & Eccleston, 2006). Furthermore, onset of new pain in women can be predicted using the number of existing pain conditions (Von Korff, Dworkin, Le Resche & Kruger, 1988).

Wise et al. (2002) found that in response to noxious thermal stimuli, women reported greater subjective unpleasantness to pain, reduced pain tolerance, and a lower mean pain threshold than men. Furthermore, pupillary dilation following painful stimulation, an indicator of acute pain, was found to be greater in women than in men (Ellermeier & Westphal, 1995). Moreover, women removed their hand from a noxious cold stimulus approximately 40% sooner than men did (Kim, et al., 2004).

Interestingly, and discrepant from animal models, women may receive greater benefit from opiate drugs because they self-administered only half as much opiate medication as men did post-surgery (Miaskowski, Gear, & Levine, 2000). Concurrently, Zubieta et al. (2002) found that after experimentally controlling pain intensity levels between men and women, the two genders still differed in the direction and magnitude of response to pain in the μ-opioid system in different brain nuclei. Furthermore, research examining pharmacokinetic drug properties suggested that the effectiveness of medication as well as tolerance to side effects may vary by sex (Gandhi, Aweeka, Greenblatt, & Blaschke, 2004). Moreover, while the perceived ability to modulate pain response was found in women but not men, the analgesic qualities of cognitive coping strategies are reversed by naloxone, an opioid antagonist (Fillingim, 2000; 49-51). Thus, men and women may not only differ in pain sensitivity, but also respond differently to both endogenous and exogenous analgesics, as well as to substances that disrupt analgesic response.

Genetic Factors

Individual variability in pain perception and response has been linked to genetic factors. For instance, individuals with a family history of pain are more likely to experience greater sensitivity to painful stimuli (Lester, Lefebvre, & Keefe, 1994; Koutantji, Pearce, Oakley, & Feinmann, 1998). Kim and colleagues (2004) were interested in examining the role of genetic factors and individual differences in human pain sensitivity to cold and thermal stimuli (Kim et al., 2004). Pain sensitivity to the cold stimulus was measured as the time it took for participants to withdraw their hand from an insulated bucket filled with cold ice water, and intensity ratings were given using a visual analogue scale (VAS). Thermal pain intensity ratings were assessed using the VAS to which participants rated their pain following the application of quasi-randomized varying levels of thermal stimuli to their forearm. Temperament was measured using the temperament and character inventory (TCI) in order to assess whether their sample of 500 subjects scored onto dimensions of persistence, reward dependence, harm avoidance, or novelty seeking (Kim, et al., 2004). Genotyping was conducted by Kim and colleagues (2004) by collecting 50 ml of venous blood from each participant, and analyzing loci in the vanilloid receptor subtype 1 gene (TRPV1), d opioid receptor subtype 1 gene (OPRD1), and catechol O-methyltransferase gene (COMT). Results showed significant interactions between the TRPVI and ORPDI single nucleotide polymorphisms and individual differences such as temperament, ethnicity, and gender to cold and thermal pain sensitivity (Kim, et al., 2004).

Specifically, there were significant gender differences for harm avoidance and reward dependence, cold withdrawal time, cold pain intensity, and heat pain intensity. Females displayed higher heat pain intensity than males at 49º C, and those who scored onto the novelty seeking dimension of the TCI showed greater pain resistance than females who placed onto the low novelty seeking group. Males who scored high on persistence in the two homozygous groups of the ORPD1 Phe27Cys genotypes demonstrated reduced thermal pain response at 49º C when contrasted with low persistence males (Kim et al., 2004). Thus, while these data confirmed gender as a significant factor in response to both cold and hot pain stimuli, temperament in the form of harm avoidance, novelty seeking, and persistence further characterized pain response (Kim et al., 2004).

Regarding ethnicity, European American subjects displayed longer cold withdrawal time than the other ethnic groups represented in the study; African Americans, Hispanic Americans, and Asian Americans. Furthermore, European American males demonstrated longer cold withdrawal time than European American females, and European males who scored low on harm avoidance showed longer cold withdrawal time than males who scored high on harm avoidance (Kim et al., 2004). Overall, the findings point to complicated interactions between genetic variation, gender, ethnicity, and temperament.

Pain sensitivity within and between individuals can vary not only by pain intensity but also by the pain stimulus itself, such that individuals that are sensitive to thermal pain may not necessarily be as sensitive to cold presser pain (Kim et al., 2004;

Coghill, 2010). Coghill (2010) suggested that while sensory differences between individuals are supported by genetic factors, they are also heavily influenced by cognitive and psychological factors.

General Psychological Factors

Psychological factors are known to affect pain perception (Dworkin & Breitbart, 2004). Grunau, Whitfield, and Petrie (1994) examined pain sensitivity and temperament in extremely low-birth-weight premature toddlers and preterm and full term toddlers. They found that parents rated the extremely low birth weight premature children, who most likely experienced the greatest amount of medical procedures as an infant, and therefore psychological trauma, significantly less sensitive to pain, with boys being the least sensitive (Grunau, Whitfield & Petrie, 1994). Pain sensitivity ratings were significantly correlated with temperament for all groups, except the extremely lowest birth weight group (Grunau, Whitfield & Petrie, 1994). Among the toddlers born at full birth weight, those highest in emotional reactivity were labeled as more sensitive to everyday pain by parents (Grunau, Whitfield & Petrie, 1994). However, early life pain sensitivity is only one of many pertinent aspects in the experience of pain. Development of pain behaviors is manifested through cultural and psychological factors.

According to McGrath (1994), pain is a complicated multifaceted perception that fluctuates in its intensity, location, length, and noxiousness, and that psychological factors such as emotion and context can alter its experience. Due to its capacity to differentially respond to equal amounts of tissue damage between and among individuals,

the nociceptive system is viewed as plastic (McGrath, 1994). Prior pain experience, cognitive level, and psychological factors mold together to change how a person may react to a noxious stimulus. Individuals' understanding of their pain source, their feelings, and behaviors in response to pain all affect their perception of pain (McGrath, 1994). Individual characteristics presumed to be stable, such as cultural and familial experiences, age, and gender, as well as unfixed contextual factors, such as emotions and behavior, join together to influence painful experiences (McGrath, 1994). The possible roles of the psychological factors of pain perception are displayed in Figure 1 (McGrath, 1994).

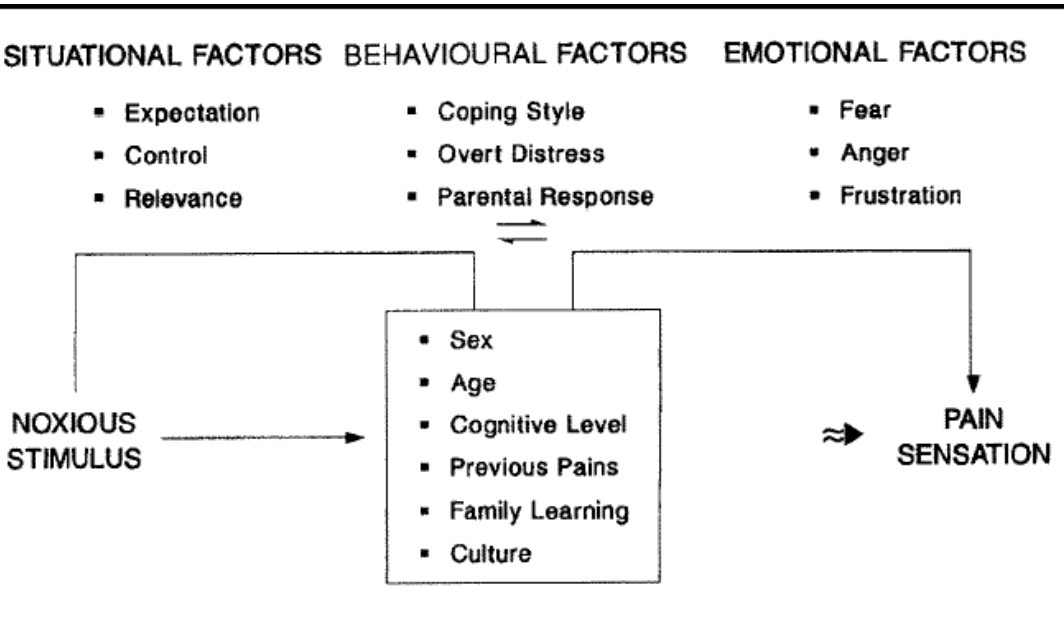

Figure 1: Roles of psychological factors in pain perception (McGrath, 1994).

As gender differences in pain sensitivity are discussed in its own section, the discussion of psychological factors on pain will not examine gender differences.

While individuals cognitively construe new experiences of pain relative to prior painful experiences, differences in pain sensitivity cannot be adequately explained by this factor alone (McGrath, 1994). Cultural and familial experiences not only shape our expressions of pain, such as crying, but also help us evaluate its severity, and adopt coping behaviors, such as whether to seek aid. While typical acute pain does not extend distress due to its occurrence from daily activities, repeated medical procedures that produce acute pain could be confounded by emotional factors, such as anxiety and expectation of pain, that may exacerbate pain perception, as emotional distress has been shown to be associated with greater sensitivity to experimental pain (McGrath, 1994). Recurrent pain is mitigated by different psychological factors than is acute pain, such as negative expectations and perceived lack of control over the painful condition and its outcome, causing significant emotional distress for patients and families.

Continuous or chronic pain may arise from both central and peripheral nociceptive mechanisms (McGrath, 1994), and these patients also suffer from emotional distress from failed treatments, as well as psychological distress from disabling chronic pain. As this literature review focuses primarily on differences in pain sensitivity, chronic pain conditions are beyond the scope of this topic. Pain sensitivity is influenced by situational factors such as awareness of the source of pain, anticipation of pain relief, perceived control, and the subjective significance of pain (McGrath, 1994). In some individuals, psychological suffering, such as anxiety, depression, and negative emotions, serves to not only increase pain sensitivity, but may also become a consequence of pain

experience (McGrath, 1994). For instance, some individuals opt to suppress their emotional distress, and instead express it in terms of somatic symptoms.

Psychopathology and Pain Sensitivity

Patients with depression and anxiety report increased pain levels, which may reflect pathology in the levels of serotonin and/or its receptors. Furthermore, depression is often comorbid with pain (Greenspan et al., 2007). In a study examining previous pain complaints and pain-thresholds in psychiatric in-patients with Major Depressive Disorder (MDD) or Panic Disorder (PD), Lautenbacher, Spernal, Schreiber, and Krieg (1999) found that both MDD and PD patients reported a significantly greater number of painful body sites, as well as significantly greater intensity and unpleasantness of pain history compared with healthy controls. The patient groups did not statistically differ from each other in pain history (Lautenbacher, Spernal, Schreiber, & Krieg, 1999). Regarding pain thresholds to pressure pain and cold-pressor pain, patients with MDD displayed significantly higher pain thresholds to pressure pain compared with PD patients and healthy controls, and significantly greater pain threshold to cold-pressor pain compared with PD patients (Lautenbacher, Spernal, Schreiber, & Krieg, 1999). Patients with PD were statistically indistinguishable from healthy controls to all three types of pain stimuli. There were no significant differences between the three groups' heat pain thresholds (Lautenbacher, Spernal, Schreiber, & Krieg, 1999).

Thus, despite reporting greater affliction from clinical pain, psychiatric in-patients with MDD displayed increased pain thresholds to noxious stimuli, while patients with PD

displayed pain thresholds comparable to those of healthy controls (Lautenbacher, Spernal, Schreiber, & Krieg, 1999). Lautenbacher and colleagues' findings in depressed patients reveal the inadequacy of defining pain perception as pain threshold, as this definition may not fully explain the expression of pain. Moreover, the researchers propose other explanations for the reported elevated clinical pain among these patients, such as emotional factors or the endogenous inhibitory pain processing for long-lasting pain, both of which were uninvestigated in this study.

Patients with PD responded normatively to noxious stimuli, and despite insufficient power, Lautenbacher and colleagues (1999) suggest a potential relationship between perceptual pain and the reported unpleasantness of clinical pain in this group, as their trait anxiousness may lead them to detect for unpleasantness in different situations. Moreover, when examining pain sensitivity in both comorbid and non-comorbid pain and psychiatric patients, Merskey (1965) found that while patients with depression with concomitant pain displayed increased pain sensitivity, patients with anxiety and concomitant pain displayed reduced sensitivity to pain. Both manuscripts demonstrate that pain complaints in psychiatric populations are multifarious, and cannot be elucidated through pain sensitivity disparities alone.

Chapter Two:

Alcohol Dependence

Distinguishing Alcohol Abuse from Alcohol Dependence/Addiction

Alcohol is a legal drug in many countries, and its intermittent use is often socially encouraged. Alcohol dependence or addiction to alcohol is distinct from the occasional use of alcohol, in that dependence is characterized by compulsive seeking, over limiting its intake, and loss of control. According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), alcohol dependence occurs when individuals continue to use alcohol in spite of significant areas of dysfunction, evidence of physical dependence, and/or associated hardship (4th ed., text revision, American Psychiatric Association, 2000). Diagnosis for alcohol dependence according to the DSM-IV-TR entails at least three of the seven following criteria to manifest within 12 months: tolerance; withdrawal symptoms; use in larger amounts than intended; persistent desire to cut down; time spent obtaining alcohol or recovering from its effects; reduction in social, occupational, or recreational pursuits due to its use; and continued use in spite of knowledge of its resulting harm. Alcohol abuse is distinguished from alcohol dependence in that individuals who abuse alcohol do not meet criteria for dependence as described above, but recurrently use alcohol in maladaptive ways that disrupt their daily functioning, and do not show evidence of tolerance or withdrawal symptoms.

Cycles of Alcohol Addiction

Drug addiction involves characteristics involved in both impulse control disorders and compulsive disorders (Koob & Volkow, 2009). Impulse control disorders exhibit an escalating sense of arousal prior to commencing an impulsive act, followed by pleasure once the impulse is acted upon. This describes the drug-seeking criterion for alcohol dependence, where alcoholics seek out the effects of alcohol for its hedonic euphoric elements, which is associated with positive reinforcement mechanisms. Positive reinforcement occurs when the presentation of a pleasant stimulus (i.e. alcohol) increases the probability of a response, as illustrated by an alcoholic continuing to seek out alcohol due to its positive effects on mood. Compulsive disorders, in contrast to impulsive disorders, exhibit anxiety or negative affect prior to commencing a repetitive behavior, followed by relief from enacting the compulsive behavior. This describes the withdrawal and tolerance symptoms of alcohol addiction, whereby an alcoholic compulsively seeks out alcohol to relieve themselves of withdrawal symptoms or negative affect, which is associated with negative reinforcement. In contrast to positive reinforcement, negative reinforcement occurs when the removal of an aversive stimulus (i.e. withdrawal symptoms) increases the likelihood of a response, as illustrated by an alcoholic compulsively seeking out alcohol to reduce symptoms of withdrawal. Impulsivity and compulsivity form the cycles of alcohol addiction, where impulsivity predominates during the earlier stages of addiction and impulsivity combined with compulsivity governs the later stages. According to Koob and Volkow (2009), three stages describe the addiction cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/

anticipation/craving, and alcohol addiction occurs when these three stages spiral and increase in intensity (Koob & Le Moal, 1997).

Rates of Alcohol Dependence

According to the World Health Organization (WHO), alcohol addiction is a global problem, as stated in the report "Management of substance abuse: Alcohol" (2014), alcohol kills approximately 2.5 million people per year at present, which classifies alcohol as the third leading risk factor worldwide for disability and death. In the Western Pacific and Americas geographical regions, it is the number one factor, while it sits at number two in Europe. In 2012, it was estimated that of U.S. citizens over the age of 12, 52% (135.5 million) drank alcohol, with 8.5% (22.2 million) meeting criteria for alcohol abuse or dependence (Substance Abuse and Mental Health Services Administration, 2012). Thus while alcohol is legal, it is one of the nation's largest drug problems whether measured in terms of mortality, morbidity or social cost. The fact that it is commonplace to separate alcohol from illegal drugs in our everyday speech obscures the concerns that alcohol shares with other drugs of abuse, and reduces society's awareness of the grave problems associated with alcohol dependence, which in turn hinders the prevention and treatment of alcohol dependence (Institute in Medicine, 1996).

Treatment

The need for treatment is apparent for individuals diagnosed with alcohol dependence. Three types of treatment for alcohol addiction are pharmacological, in-patient and outpatient care at a rehabilitation facility, and community support groups such as Alcoholics Anonymous (AA). Benefits of treatment beside alcohol cessation include improved health and increased productivity. Alcohol dependence is typically a chronically relapsing disorder owing to the compulsive drug-seeking behavior and loss of control over consumption. Although research has demonstrated that treatment for drug abuse is cost effective in decreasing consumption and its associated social and health consequences (Institute in Medicine, 1996), few individuals enroll in a treatment facility. According to the National Institute on Drug Abuse (NIDA), there continues to be a large treatment gap in the US, where in 2012, only 2.5 million people (1 percent) of an estimated 23.1 million Americans (8.9 percent) who required treatment related to alcohol or drugs actually received treatment at a special facility. Furthermore, rehabilitation methods have not proven highly successful, as relapse rates are alarmingly high, estimated at 60% one year after receiving a minimum 90-day treatment in a study on adolescents (Hser, et al., 2001), which is unsurprising as chronic relapse after prolonged abstinence is a hallmark of addiction (Koob & Volkow, 2009). In adults who received treatment at a rehabilitation facility, estimated long-term relapse rates have varied between 20 and 80% (Jin, Rourke, Patterson, Taylor, & Grant, 1998; Finney, Moos, & Timko, 1999). The alarming rate of relapse post treatment may be due to its limited duration, as most rehabilitation facilities traditionally offer 28 or 30-day treatments, and

research has shown that a minimum of three months is necessary to achieve any sort of efficacy (Simpson, Joe, Fletcher, Hubbard, & Anglin, 1999). Relapse describes the return to drug use despite attempts to remain abstinent. As it is problematic to study relapse in animal models, the neurobiological mechanisms underlying relapse are largely unknown, making it difficult to prevent and to treat relapse (Institute in Medicine, 1996).

Research on treatment research has increased the variety of pharmacotherapeutic and psychosocial treatment approaches, and the majority of treatment facilities employ both treatment methods (Institute in Medicine, 1996). Pharmacotherapy treatment methods include several drugs that have been found effective at helping with alcohol addiction, the most used being naltrexone, an opiate antagonist. Opiate antagonist medications work by binding to the opioid receptor site, thereby blocking receptor activation by alcohol, and thus preventing its euphoric and dependence-producing results. This blockade denotes competitive antagonism, and as a result, its medical efficacy may be altered by the dose of the antagonist, the time since the antagonist was taken, and alcohol dosage. Beside preventing the euphoric and thus reinforcing effects of alcohol, naltrexone has also been shown to decrease relapse to alcohol, as half of naltrexone treated alcohol dependent outpatients relapsed compared to nearly all (95%) of placebo exposed patients (Volpicelli, Alterman, Hayashida, & O'Brien, 1992). However, these relapse rates are in outpatients who consumed any alcohol while attending outpatient treatment. Differences in placebo and naltrexone treated outpatients who were abstinent during outpatient treatment are less sizeable; 23% of naltrexone treated patients relapsed compared to 54.3% of placebo treated patients. Thus, while treatment with naltrexone has

been demonstrated to be superior to placebo (Streeton & Whelan, 2001), many alcoholics continue to relapse.

As part of a multiple treatment approach, therapists routinely refer alcohol dependent individuals to Alcoholics Anonymous (AA), which uses abstinence and seeking out a 'higher power' to help prevent relapse. There is strong support for this type of 12-step approach to trying to help addiction, as well as a spiritual approach in general, among staff members at alcohol rehabilitation centers. While AA does not appeal to all alcoholics, its approach has been touted as successful with many. Interestingly, scientists tend to endorse this type of approach less, including rehab facilities in general, preferring a pharmacotherapy approach instead (Forman, Bovasso, & Woody, 2001).

Thus, while there are available treatments for alcohol dependence that hold promise for some individuals, many individuals continue to suffer from the paralyzing spiral of alcohol addiction. One theory of why current treatments are not more effective is that alcohol dependence is commonly treated as an acute illness, while instead it should be treated as a chronic medical illness, as alcohol dependence shares a common etiology with many chronic illnesses (McLellan, Lewis, O'Brien, & Kleber, 2000). The persisting challenge to alcohol treatment research is to generate additional effective pharmacotherapeutic and psychosocial treatments that are not only cost-effective, but which are tailored to the unique needs of individual patients (Institute in Medicine, 1996).

Addiction Vulnerability

Investigating the risk or vulnerability for addiction may provide several insights that have clinical implications. Firstly, such findings can help us to identify those at risk for developing alcoholism and institute preventative treatments. Secondly, as alcohol is a chronic relapsing disorder, individuals who attain abstinence may continue to have underlying vulnerabilities to relapse and by addressing them, we may increase the effectiveness of treatment. Risk focused approaches are suggested to be the most promising strategies for the effective prevention of substance abuse (Dawkins, Catalano & Miller, 1992). Overwhelmingly, the majority of research on risk factors or vulnerability for alcohol dependence has pointed to having a positive history of familial alcoholism, earlier drinking onset and specific personality traits. Additional risk factors include physiological vulnerabilities such as biochemical markers and metabolic variations.

1. Familial Heritability

While prior research has indicated that the onset of drinking at an earlier age was a significant risk factor for alcohol dependence in adulthood, Prescott and Kendler (1999) found that the relationship between early drinking and later alcohol dependence is due to familial causes, which represent both shared genetic and environmental factors. In a review on the familial incidence of alcoholism, Cotton (1979) concluded that alcoholics were more than six times as likely to be positive for a parental history of alcoholism

when compared to non-psychiatric patients, and more than twice as likely to report having an alcoholic parent when compared with non-psychiatric patients. The elevated rate of alcohol addiction among children of alcoholics indicates family history to be one of the most powerful predictors of risk for alcohol dependence, which is partially due to genetic influences (Merikangas, 1990). However, in a study examining concordance rates for alcoholism among monozygotic and dizygotic twins, Pickens and colleagues (1991) found genetic factors to have only a modest influence on overall risk for alcohol dependence, suggesting that non-biologically transmitted family characteristics may play a substantial role in imparting alcohol addiction. For instance, the mores and behaviors of family members and influential community members reinforce the already reinforcing properties of alcohol, which poses an underlying risk for the maintenance of abstinence in those attempting to recover.

Thus, the mechanisms by which familial factors dispatch increased risk for alcoholism are yet to be determined. As family studies cannot distinguish genetic from environmental influences on the development of alcohol dependence, cross-adoption studies provide the clearest model by which to disentangle gene from environmental effects. Cross-adoption studies allow us to compare rates of alcoholism in children of alcoholics (i.e. those at increased risk for alcoholism) raised by non-alcoholic foster parents with those of children of non-alcoholic parents (i.e. those not at increased risk for alcoholism) raised by alcoholic foster parents. Cross-adoption studies have shown that children of alcoholics, although raised by nonalcoholic parents, retained a significantly increased risk for alcoholism, supporting genetic over environmental effects for the

development of alcohol dependence (Goodwin, Schulsinger, Hermansen, Guze, & Winokur, 1973; Goodwin et al., 1974; Cadoret, Cain, & Grove, 1980).

2. Personality Traits and Distinct Subgroups

Personality factors may affect the induction of first alcohol use as well as regulate the progression of alcoholism. Original groundbreaking research on alcohol dependence unveiled that antisocial and aggressive behavior in childhood among boys was significantly associated with alcoholism in adulthood (McCord & McCord, 1960; McCord, 1981). More recent work by Kellam, Brown, and Ensminger (1983) found that heavy alcohol use in adolescence was predicted by aggressive behavior displayed in the first grade. Additional personality traits such as aggressiveness and neuroticism were found to be directly associated with later substance abuse (Tarter, 1988). The relationship between family history of alcoholism, alcohol use, and antisocial personality disorder in a sample of young non-alcoholic males was explored by Hesselbrock and Hesselbrock (1991). Findings indicated that while interestingly, family history of alcoholism failed to differentiate participants on these factors, participants diagnosed with antisocial personality disorder reported greater frequency of behavior problems as children related to impulsivity and conduct problems, reported drinking at a younger age, and exhibited higher scores on an alcohol screening test when compared with non-diagnosed participants. These findings suggest that antisocial personality disorder may be its own unique risk factor for developing alcohol addiction.

Different studies have shown that while impulsive and antisocial traits preceding alcoholism are found in the majority of early onset drinkers, rates are significantly lower in later onset alcoholics (Jones, 1968; Hagnell, Lanke, Rorsman, & Ohman, 1986). As there is great deal of heterogeneity among individuals afflicted with alcohol addiction, examining subgroups may shed light on different vulnerability factors as well as in assisting in the formation of targeted treatments and interventions.

Research on alcoholism has consistently recognized the existence of two types of alcoholism: Type 1 or Type A and Type 2 or Type B, as noted in the literature, whereby Type 1 alcoholics are characterized by later age of drinking onset, fewer risk factors from childhood, and fewer problems related to alcohol but greater incidence of psychopathology relating to anxiety and neuroticism, and Type 2 alcoholics are characterized by earlier onset of drinking, greater incidence of childhood risk factors, increased severity of alcohol related problems, and an greater history of receiving treatment in spite of starting to drink while younger (Jellinek, 1960; Cloninger, 1987; Cloninger, Sigvardssin, & Bohman, 1988; Babor et al., 1992; Hawkins, Catalano & Miller, 1992).

Cloninger (1987) originally differentiated the two groups according to alcohol symptom clusters and alcohol transmission patterns derived from adoption studies, and further refined the two groups according to the personality traits of novelty seeking, harm avoidance, and reward dependence. Type 1 alcoholics are depicted as dependent on social approval, therefore displaying high reward dependence; cautious, therefore displaying

high harm avoidance; and dislike taking risks, therefore displaying low novelty seeking. Unlike Type 1 alcoholics, Type 2 alcoholics are characterized by social detachment or antisocial personality; therefore displaying reduced reward dependence; confidence and lower inhibition, therefore displaying low harm avoidance; and impulsivity or excitability, therefore displaying high novelty seeking. The differentiating attributes of the two types of alcoholism proposed by Cloninger (1987) are presented in Table 1.

Characteristic features	Type of alcoholism	
	Type 1	Type 2
Alcohol-related problems		
Usual age of onset (years)	After 25	Before 25
Spontaneous alcohol-seeking (inability to abstain)	Infrequent	Frequent
Fighting and arrests when drinking	Infrequent	Frequent
Psychological dependence (loss of control)	Frequent	Infrequent
Guilt and fear about alcohol dependence	Frequent	Infrequent
Personality traits		
Novelty seeking	Low	High
Harm avoidance	High	Low
Reward dependence	High	Low

Table 1. Distinguishing characteristics of two types of alcoholism (Cloninger, 1987).

It is important to take note of Cloninger's (1987) assertion that these alcoholic subgroups should not be regarded as distinct entities of disease as many alcoholics demonstrate features of each type, but to recognize that these subgroups may represent opposing spectrums of personality traits that may develop as a result of divergent alcoholism trajectories. To illustrate, Type 1 alcoholism corresponds to drinking onset in late adulthood which is comprised of heavy drinking that is socially reinforced, and is

thus associated with a loss of control over drinking, and guilt and fear about developing dependence. Type 2 alcoholism, in contrast, corresponds to an early onset of alcohol seeking behavior without consideration of actual or potential consequences, such as driving under the influence, fighting, and recurring impulsive-aggressive conduct, and is thus associated with an incapacity to abstain (Cloninger, Sigvardssin, & Bohman, 1988).

Cloninger, Sigvardssin, & Bohman (1988) investigated personality traits in children who were later reassessed for alcoholism as adults. They found that high novelty-seeking and low harm avoidance predicted alcohol abuse at an early age, and that the risk of alcohol abuse ranged from 4% to 75% depending on childhood personality, with high-novelty seeking and low harm avoidance predicting a 19-fold increase in risk for alcohol abuse. Furthermore, their results were consonant with the typology model of alcoholism as the relationship between personality traits and risk for alcoholism was strongest for Type 2 alcoholics.

Babor and colleagues (1992) found that these two different types of alcoholics showed differences in treatment outcome, suggesting that researchers and clinicians may benefit from utilizing this dichotomized approach for designing individualized treatments. Fittingly, in an effort to evaluate the utility of this typology approach for matching patients to more effective treatments, male alcoholics were randomly assigned to receive either coping skills training or interactional group psychotherapy. It was found that Type A alcoholics benefited more from interactional group therapy, than coping skills training, and conversely, Type B alcoholics demonstrated greater improvement

from training in coping skills than from attending group therapy (Litt, Babor, DelBoca, Kadden & Cooney, 1992). Notably, these differences in treatment response were sustained for two years.

3. Addiction Vulnerability in an Already Vulnerable Population: Adolescents

Predominantly, research on drug prevention focuses on adolescents as they comprise a population most at risk for developing drug abuse and dependence since adolescence is usually the period when most begin to experiment and sample substances and when they are most susceptible to the influence of peers. Hawkins, Catalano and Miller (1992) reviewed the risk factors as well as protective factors for alcohol abuse in adolescence. Some of the identified precursors of adolescent drug abuse include drug availability, early drug use initiation, economic hardship, disordered neighborhood, and psychological characteristics; such as hyperactivity, aggressive behavior in boys, conduct problems, and family risk factors such as low-bonding, high incidence of conflict, and a family history of alcoholism and parental use of illegal drugs. The protective factors identified were not nearly as comprehensive; there was some evidence that individual attributes such as self-efficacy and positive temperament, and ties to mainstream society, may protect against drug abuse. Thus, additional research is necessary to discern auxiliary protective factors, as well as to discover the relationships between risk and protective factors, as protective factors may serve as mediators or moderators of risk, especially for risks that are immutable.

As research on different risk factors for alcoholism may vary continuously within approximately normal populations, clinicians and researchers are advised to conceptualize risk for alcoholism in degrees of probability for alcohol dependence instead of differentiating individuals simply as ‘at risk’ or ‘not at risk’ (Cloninger, Sigvardssin, & Bohman, 1988).

4. Physiological Vulnerabilities

4.1 Monoamine Oxidase is a Biomarker for Alcoholism

Physiological influences that may increase an individual’s susceptibility to alcohol addiction may include neurochemical system impairment and elevated drug susceptibility due to one’s own unique biochemistry. Monoamine oxidase (MAO) is an enzyme vital for the metabolism of a wide range of neurotransmitters in the brain such as serotonin, norepinephrine, and dopamine, and is an extensively studied biological marker for alcoholism. An assortment of research studies have found reduced platelet MAO activity among abusers of alcohol (Tabakoff et al., 1988; von Knorring, Bohman, von Knorring & Oreland, 1985; Pandey, Fawcett, Gibbons, Clark & Davis, 1988).

Tabakoff and colleagues (1988) failed to locate significant differences in MAO activity between alcoholics and controls, but alcoholics demonstrated increased rates of MAO platelet inhibition after being administered alcohol. An innovative study investigated whether MAO platelet levels differed between Type I or Type II alcoholics (von Knorring, et al., 1985), the same subgroups as described above. Findings indicated

platelet MAO activity levels effectively distinguished between the two the two types of alcoholism, supporting its role as a biomarker for alcohol addiction. When compared with healthy nonalcoholic individuals, platelet MAO activity was low in Type II alcoholics, but normal in Type I alcoholics. Moreover, first-degree relatives of participants with Type II alcoholism exhibited greater rates of alcoholism and depression than relatives of Type I alcoholics. Similarly, Pandey and colleagues (1988) found that alcoholics who exhibited low MAO platelet levels were younger in age, had an earlier age of onset of alcoholism, and had increased incidence of alcoholism in the family, echoing the characteristics of Type II alcoholics. This suggests that Cloninger's (1987) subdivision of alcoholism into two types appears to bestow merit for future studies interested in examining the underlying causes of alcoholism and its treatment.

4.2 Metabolic Variations

Efficient metabolism of alcohol may increase the risk for alcohol dependence by permitting increased amounts for digestion, and thus may mediate the transition from alcohol abuse to alcohol dependence. Schuckit (1984, 1985) studied the effects of alcohol on young men who consumed alcohol but who did not meet criteria for alcohol disorders, and who were categorized as at risk for developing alcohol dependence due to having a family history of alcoholism. The earlier study found that men at risk for alcoholism described fewer acute feelings of subjective intoxication after drinking, when compared with similarly matched men who did not have an alcoholic first degree relative (Schuckit,

1984). In the latter study, Schuckit (1985) investigated physical indicators of alcohol intoxication by indexing level of body sway and found that men with a family history of alcoholism displayed significantly less body sway after consuming alcohol than men without a history of alcoholism in their family. The dual findings of decreased intensity of both subjective and physical reactions to alcohol in those at risk for alcoholism provide support for efficient metabolism to be a marker for susceptibility toward developing alcohol dependence.

On the other hand, less efficient metabolism of alcohol may serve as a protective factor against developing alcohol dependence. For example, many Asians are biologically buffered from becoming alcohol dependent due to a polymorphism of liver enzymes that Caucasians don't manifest (Yoshida, 1983; Higuchi et al., 1995; Yoshida, 1994). One of these liver enzymes, the inactive form of alcohol dehydrogenase-2 (ADH2) permits high levels of acetaldehyde to accrue in the blood subsequent to alcohol ingestion, which causes an adverse reaction in the form of a flushing response, which generates a protective influence by preventing further alcohol ingestion, and may reduce risk for developing alcoholism (Thomasson et al., 1991; Bosron & Li, 1986).

Thus, the inability to metabolize alcohol may serve as a protective factor, especially when exposure to alcohol is recurring, while the efficient metabolism of alcohol allows for increased alcohol consumption that may increase susceptibility for alcohol addiction or facilitate the transition from alcohol abuse to dependence.

Chapter Three:

Link between Pain Sensitivity and Alcohol Addiction

Alcohol Dependence and Pain

According to Ilgen and colleagues (2010), there are several hypotheses explaining the concurrence of alcohol dependence and pain including self-medication, stress-diathesis, and common underlying risk factors. A unique comorbidity hypothesis is unlikely appropriate, as while some research has shown chronic pain to be a risk factor for substance use disorders (Brown et al., 1996; Larson et al., 2007), others have demonstrated that substance use disorders predate pain conditions (Dersh et al., 2007). These compound findings elicit inquiry as to whether pain sensitivity triggers alcoholism or vice-versa.

1. Analgesic Effects of Alcohol

Reports show that as many as a quarter of individuals experiencing pain self-medicate with alcohol (Riley & King, 2009). Wolff, Hardy, and Goodell (1942) found that alcohol increases pain thresholds up to 45% above baseline pain levels. A review by Pihl and Peterson (1992) showed evidence that alcohol administered at pharmacological dosages has analgesic effects, and that these effects negatively reinforce drinking because alcohol reduces pain and discomfort. Thus, individuals who drink alcohol experience pain reduction, making them more likely to drink when in pain, demonstrating alcohol's negative reinforcement properties. Pihl and Peterson (1992) suggest that alcohol is most

reinforcing to individuals with greater sensitivity to pain. The pleasant hedonic state conferred by addictive substances is related to the neutralization of pain, as related neuroreceptor systems are implicated in both alcohol's reinforcing effects and its analgesic consequences (Le Magnen et al., 1980), discussed in its own section below.

In an effort to alleviate undertreated pain, individuals seeking out the analgesic quality of drugs are described as pseudoaddicts (Weissman & Haddox, 1989). Although pseudoaddicts display medication-seeking behavior that mirrors true addiction behavior, they are driven to obtain substances to relieve pain, as opposed to obtain substances to abuse. Nevertheless, it is likely for individuals to transition from pseudoaddiction to true alcohol dependence as extensive experience with alcohol has led users to expect pain relief (Cutter et al, 1976), and evidence suggests that individuals favored alcohol dosage may provide the greatest amount of pain relief (Brown & Cutter, 1977). Thus, the analgesic effects of alcohol may cause individuals to become susceptible to dependence.

2. Hyperalgesic Effects of Alcohol

Increased pain in alcoholics may be explained by withdrawal mechanisms, peripheral neuropathy, or the existence of chronic pain. The link between pain sensitivity and addiction to alcohol is complex in that alcohol use in humans not only reduces their sensitivity to pain due to its analgesic qualities as described above, but withdrawal from chronic alcohol consumption frequently increases pain levels, as part of withdrawal mechanisms. Furthermore, patients characterized with greater severity of withdrawal displayed reduced pain threshold and tolerance (Jochum, Boettger, Burkhardt, Juckel, &

Bar, 2010). Similarly, when deprived of alcohol, ethanol dependent rats display attenuated nociceptive thresholds when compared to non-dependent controls (Dina, Messing, & Levine, 2006).

Chronic alcohol consumption has been shown to influence the development of neuropathic pain in the duration of its use (Koike et al., 2003; Zambelis, Karandreas, Tzavellas, Kokotis & Liappas, 2005). Moreover, the development of neuropathic pain during alcohol withdrawal may signify a crucial symptom that distinguishes alcohol dependent individuals from alcohol abusers (Diamond & Messing, 1994). Alcohol withdrawal can further exacerbate neuropathy (Dina et al., 2006). The research described above may indicate that desire to lessen the effects of hyperalgesia induced by withdrawal is a motivational factor for continued drinking. The current literature has not addressed if alcohol induced neuropathic pain is also attenuated by alcohol in chronic alcoholics.

While not addressed in detail in the pain sensitivity section above, it is important to examine the relationship between chronic pain and alcoholism. While it is claimed that a significant percentage of chronic pain patients are afflicted with drug addiction, Fishbain, Rosomoff and Rosomoff (1992) investigated its veracity by reviewing relevant articles. They found that among chronic pain patients, the prevalence percentages for diagnosed drug addiction ranged from 3.2% to 18.9%, but that there is at best only modest support that chronic pain patients exhibit addictive behaviors. Thus, it remains unclear whether alcohol use influences the development of chronic pain.

3. Mixed Effects of Alcohol

Alcohol use normalizes pain and perceptions of discomfort in excessive alcohol users, as they are more sensitive to painful stimulation, and experience greater pain reduction after imbibing (Stewart et al., 1995). However, continuing alcohol use can induce symptoms of pain, and may worsen chronic pain stemming from other sources (Egli, Koob & Edwards, 2012). Thus, while individuals in pain may seek out the analgesic effects of alcohol, the continued use of alcohol may exacerbate pain, further complicating the question as to whether pain leads to addiction or vice-versa.

In a longitudinal study following older community residents, Brennan, Schutte, and Moos (2005) showed that problem drinkers reported increased severity of pain symptoms and a higher frequency of self-medication with alcohol, when compared to non-problem drinkers,. Interestingly, both baseline levels of increased body pain and increased drinking problems independently predicted increased self-medication with alcohol, suggesting that pain and alcohol abuse both lead to increased frequency with which alcohol is used to manage pain. Additionally, a significant statistical interaction between the number of drinking problems and pain severity independently predicted alcohol self-medication among problem and non-problem drinkers (Brennan et al., 2005; See Figure 2).

At higher levels of pain, self-medication was more likely to occur among both problem and non-problem drinkers. Nevertheless, this effect was most pronounced among problem-drinkers. Furthermore, findings displayed a significant interaction

between the use of alcohol to manage pain on chronic health problems and baseline drinking problems among men (Brennan et al., 2005; See Figure 3).

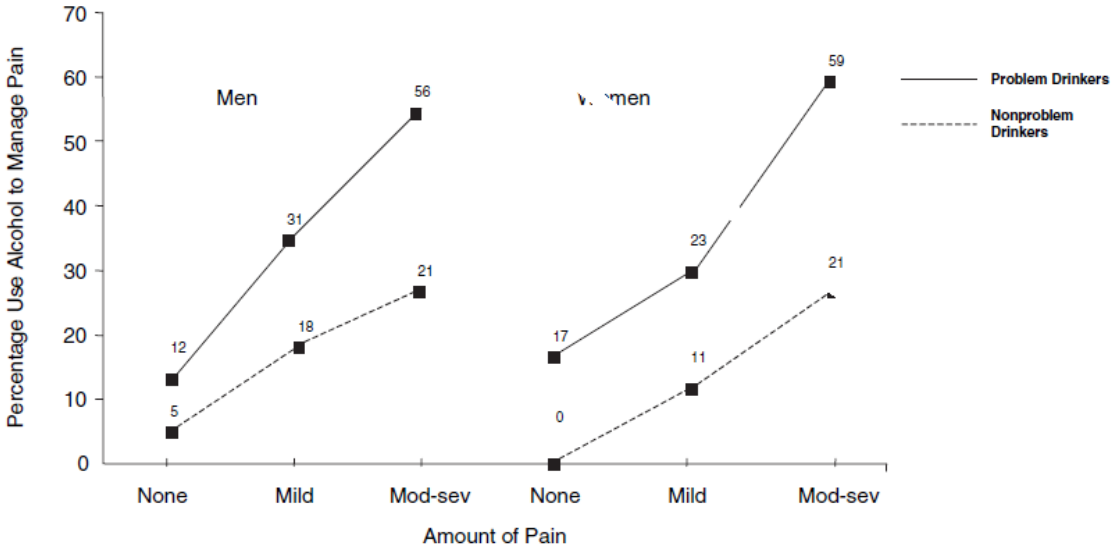

Figure 2: Use of alcohol to manage pain among problem and non-problem drinkers (Brennan et al., 2005).

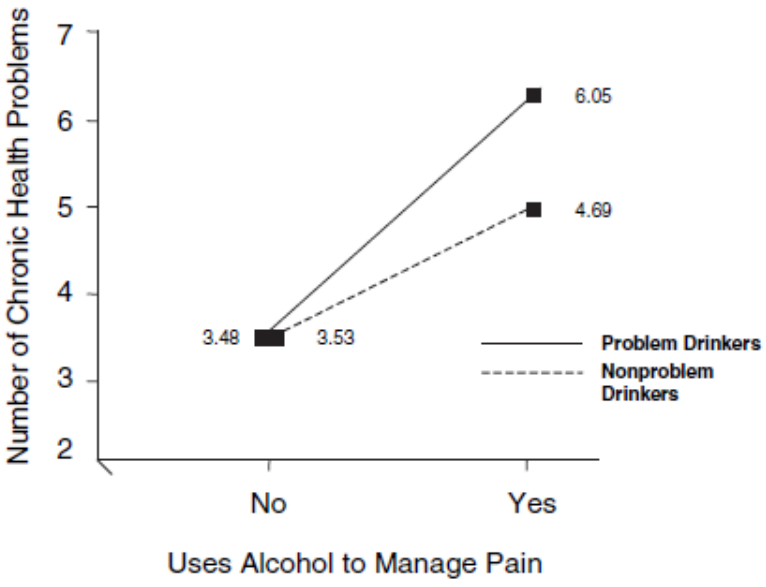

Figure 3: Interaction of drinking problems and use of alcohol to manage pain on chronic health problems among men (Brennan et al., 2005).

Moreover, three years later, persistent self-medication with alcohol in problem drinkers caused an exacerbation of drinking and health problems. Conversely, individuals who discontinued the use of alcohol to manage pain drank less at follow-up. These individuals may have diminished their risk for additional future health problems. These findings may point to a complicated relationship between pain and alcoholism whereby increased pain leads individuals to drink, and those who continue to drink to manage pain experience greater health problems, resulting in more pain. Brennan and colleagues (2005) recommend screening for alcohol dependence in older adults as their findings suggest that older individuals with drinking problems are at greater risk for self-medicating with alcohol to manage pain, which can cause greater health problems.

Jochum and colleagues (2010) investigated pain perception, pain threshold, and pain tolerance among alcoholics undergoing withdrawal at admission for treatment, at discharge, abstinent alcoholics, and normal controls. While not discussed in detail, they found that abstinent alcoholics most resembled healthy controls in that they exhibited greater thermal pain threshold and pain tolerance than alcoholic patients. This suggests that the hyperalgesic effects of alcohol can disappear after a period of abstinence.

Neural Mechanisms Involved in Pain and Alcohol Addiction

1. Neuroreceptors and Neurotransmitters

In a review on the reciprocal relationship between alcohol dependence and pain, Egli, Koob, and Edwards (2012) discuss how similar neuroreceptor systems implicated in pain transmission are also implicated in alcohol addiction. Neurons responsive to pain are

plentiful in the lateral part of the central amygdala (Bernard & Besson, 1990). Alcohol causes the release of several neurotransmitters in the central nucleus of the amygdala such as GABA, dopamine, and serotonin (Yoshimoto et al., 2000). Drugs of abuse such as alcohol promote the release of dopamine into the nucleus accumbens (NAc), and while the exact mechanisms are unclear, the release of dopamine along the mesolimbic pathway is presumed to account for encouraging the reinforcing effects of such substances (Boileau et al., 2003; Pierce & Kumaresan, 2006). Similarly, following the offset of pain stimulation, fMRI studies have shown increased activation relative to baseline in the NAc (Becerra & Borsook, 2008).

Neugebauer and colleagues (2003) found that upregulation of presynaptic metabotropic glutamate receptors is necessary for the increased excitatory neurotransmission in the central nucleus of the amygdala, often called the nociceptive amygdala, which is associated with pain related neuroplasticity in arthritis patients. Alcohol has been shown to amplify glutamate levels in the central nucleus of the amygdala in animals that are alcohol dependent (Roberto et al., 2004). Similarly, arthritic animals show increased excitation in this region, which is reduced after receiving corticotrophin releasing factor (CRF1) receptor antagonists (Ji & Neugebauer, 2007). This suggests that the amygdala and the release of several neurotransmitters in that region are related to the modulation of pain levels as well as being affected by drug dependence.

Increased glutamatergic transmission in the NAc is also implicated in the development of addiction (Apkarian et al., 2013). Blockade of the CRF1 receptor, commonly associated with stress behaviors also alleviates hypersensitivity of pain in

animal models (Hummel et al., 2010) including hyperalgesia during alcohol withdrawal (Edwards et al., 2012). In humans, CRF function is activated during acute withdrawal from alcohol, and therefore may mediate facets of stress related to abstinence (Koob, Heinrichs, Menzaghi, Pich, & Britton, 1994). Moreover, human patients expecting pain diagnosed with irritable bowel syndrome displayed reduced limbic over-reactivity in the insula, anterior cingulate cortex, and amygdala when administered CRF1 blockade (Hubbard et al., 2011).

1.1 Neuroreceptors Implicated in Withdrawal and Hyperalgesia

Neuroadaptations within the central nervous system (CNS) must occur to maintain functioning in the brain during alcohol dependency, and further adjustments between excitatory and inhibitory neural mechanisms take place during alcohol withdrawal (Jochum et al, 2010). GABA is the main inhibitory and glutamate is the main excitatory neurotransmitter in the mammalian cortex (Petroff, 2002). While the research on neural substrates of alcohol withdrawal is limited, neuropharmacological mechanisms such as a decrease in GABAergic function and an increase in glutamatergic function has been found (Grant, Valverius, Hudspith, & Tabakoff, 1990). Mhatre and colleagues (1993) propose that hyperalgesia during alcohol withdrawal may be due to the inhibition of GABA-A receptor activity. Correspondingly, increased transmission of glutamate, the metabolic precursor of GABA (Petroff, 2002), may be linked to pain sensitization, as indicated in opioid induced hyperalgesia (Simonnet & Rivat, 2003). These findings seem to suggest that GABA related neuroreceptors and neurosynaptic pathways provide a key

link between the pain related effects of alcohol and the mechanisms involved in alcohol dependency.

2. Neural Circuitry

Parallel central reward brain circuitry involving the nucleus accumbens (NAc), medial prefrontal cortex (mPFC), and emotion circuitry such as the amygdala and insula, implicated in addiction, are also important in the development of pain pathology (Apkarian et al., 2013).

2.1 Amygdala and Medial Prefrontal Cortex (mPFC)

Apkarian and colleagues (2013) propose a model linking the mPFC and the amygdala, a region essential for emotional processing, whereby abnormal amygdala activation instigates the affective facets of pain, disrupting important mPFC functioning necessary for emotional processing and decision-making. Dysfunction of the mPFC is a biomarker of behavioral disinhibition, a key characteristic in drug addiction. Several studies have established correlations between amygdala activity and pain response (Neugebauer, Weidong, Bird & Han., 2004; Neugebauer, Galhardo, Maione & Mackley, 2009). Moreover, it has been shown that pain can be elicited or increased in animal models even in the absence of tissue damage by increasing amygdala activation (Bourbia Ansah, & Pertovaara, 2010; Myers & Greenwood-Van, 2010).

2.2 Connectivity between Nucleus Accumbens (NAc) and mPFC

In a groundbreaking study, Baliki and colleagues (2012) found that significant differences in brain gray matter density and level of functional connectivity between the mPFC and NAc predicted long-term pain trajectory, and differentiated chronic pain patients from those who recovered. It was inferred that the degree of exchange between the mPFC and NAc pointed to the hyperexcitability of mesolimbic circuitry, leading to cortical reorganization, and facilitated unremitting pain in some patients. One study implicating the NAc as central to both pain and addiction showed that the NAc was activated by cues predicting pain, and that dopaminergic inputs to the NAc signal both punishment and reward, which are implicated in addiction processes (Ungless, Magill, & Bolam, 2004). Moreover, human and animal models of addiction have established that dysregulation of the NAc-mPFC reward circuitry is important in the development of drug addiction (Kalivas & Volkow, 2005). For instance, it has been shown that this NAc-mPFC circuitry is involved in the transition from recreational drug use to drug addiction (Kalivas & Volkow, 2005).

2.3 Insular Cortex

Chronic back pain patients showed decreased gray matter density in the right insula and reduced functional connectivity between the insula and the dorsolateral prefrontal cortex and precuneus (Baliki et al., 2012). This reduced functional connectivity was negatively correlated with pain intensity, but positively associated with gray matter density in the insula (Baliki et al., 2012). Baliki and colleagues (2012) interpret these

findings in that the persistence of pain may be directly related to functional reorganization of the insula. Naqvi and colleagues (2007) implicated the role of insula in addiction by showing that smokers with brain damage to the insula found quitting smoking to be easier. According to Tracey (2011), functional neuroimaging studies pinpoint the insular cortex as the most regularly activated region in pain studies in humans. When anticipating rewards or losses, individuals with a positive family history for alcohol addiction and a variant of the GABA2 gene display elevated responding in the insula (Villafuerte et al., 2012).

Genetic Influences on Pain and Alcohol Addiction

1. Genetic Heritability

Stewart, Finn and Pihl (1995) found that men high in risk for alcoholism, as determined by genetic load, rated electric shock as more painful than low risk controls. However, these effects disappeared when administered pharmacologically significant levels of alcohol, demonstrating the "normalizing" effect of alcohol on pain. These findings are consistent with the work of Brown and Cutter (1977), who found that alcohol increases problem drinkers' ability to cope with pain. However, unlike Brown and Cutter (1977), the findings of Stewart, Finn and Pihl (1995) showed no group differences between men at high risk versus those low in risk for alcoholism in weekly alcohol consumption, and that pain ratings were uncorrelated with dosage consumed. The investigators proposed that men with a multigenerational history of alcoholism were likely to be more sensitive to pain prior to alcohol initiation. Thus, men higher at risk for

alcoholism may be more sensitive to pain due to genetic factors or to having been brought up in a disordered family atmosphere (Stewart, Finn & Pihl, 1994). The negative reinforcing effects of alcohol, whereby alcohol intake is more likely to take place in order to avoid pain, may be mediated by the opiate system (Altshaler et al., 1980).

2. Genetic Variation

The pathophysiology of substance dependence including alcohol addiction is associated with the endogenous opioid system (Bodnar & Hadjimarkou, 2003). OPRM1, a gene that codes for μ-opioid receptors has been identified as a candidate gene for developing addiction including alcohol dependence, and ranks highly according to criteria prioritizing it as a candidate gene in studies on pain (Ray & Hutchison, 2004; Belfer et al., 2004, respectively). While there has been no study to date examining the effects of OPRM1 genotype on alcohol addiction and pain sensitivity simultaneously, Ray and Hutchison (2004) investigated associations with alcohol sensitivity, and Fillingim and colleagues (2005) examined associations with pain sensitivity.

Ray and Hutchison (2004) investigated whether alcohol sensitivity is associated with specific variants of the A118G functional polymorphism of the OPRM1 gene, as prior work has shown the G variant to demonstrate a significantly stronger affinity than the A variant for binding with β-endorphin, an endogenous opioid which activates the μ-opioid receptor (Bond et al., 1998). Methodology important to the Ray and Hutchison (2004) study included administering alcohol intravenously to participants, and isolating genomic DNA from buccal cells via cheek swabbing. As expected, findings indicated

greater reported sensation of euphoria, stimulation, and intoxication across increasing breath alcohol concentration trials among individuals heterozygous for the G allele (AG) of the OPRM1 gene when compared with homozygous A (AA) allele individuals (Ray & Hutchison, 2004). Importantly, there were no differences between the groups on measures of drinking problems, frequency, or episodes.

Interestingly, Ray and Hutchison (2004) found that G allele carriers were three times more likely than homozygous A allele participants to report a family history positive for alcoholism, suggesting that children of alcoholics may be more likely to carry the G allele. Nevertheless, controlling for family history did not alter the findings. These findings may support previous research demonstrating that naltrexone, an opiate antagonist which reduces alcohol related euphoria, to be a more effective treatment for G allele carriers than homozygous A allele individuals (Oslin et al., 2003).

Fillingim and colleagues (2005) investigated genetic contributions associated with pain perception in humans. They found that participants with the rarer G allele of the A1186 single nucleotide polymorphism of the μ-opioid receptor gene (OPRM1) exhibited significantly higher pressure pain thresholds than those homozygous for the A allele (Fillingim et al., 2005). They also found a sex by genotype interaction for G allele carriers, indicating men were less sensitive than women were to a heat pain stimulus of 49°C.

The work of the above investigators demonstrates that the A1186 variant of the OPRM1 gene is associated with sensitivity to both alcohol and pain. While Ray and Hutchison (2004) showed G allele carriers to be more sensitive to the effects of alcohol,

the findings of Fillingim and colleagues (2005) conversely displayed G allele carriers as less sensitive to the effects of pain. Although it is difficult to reconcile these counterintuitive findings, it is important to note that while Fillingim and colleagues (2005) controlled for sex in all genotype analyses, Ray and Hutchison (2004) failed to employ sex as a covariate in their analyses, as they accounted for sex by modifying alcohol concentration administrations according to the sex and weight of their participants.

Addiction to alcohol is mediated by environmental factors such as early life stress, which may influence genetic susceptibility (Clarke et al., 2011). While it is recognized that dopaminergic signaling mediates the reinforcing features of alcohol, there is limited genetic evidence for the effects of stress on alcohol reinforcement. Clarke and colleagues (2011) investigated the genetic links between early life stress and alcoholism by examining the KCNJ6, a gene that encodes GIRK2, a protein augmented by the stress peptide corticotrophin-releasing hormone (CRF). According to Ikeda and colleagues (2002), the GIRK channel is potentially one of the key molecules in furthering the understanding of the pain control system. Clark and colleagues (2011) found that the rs2836016 polymorphism of the KCNJ6 gene was associated with alcohol dependence in adults, and then in a subsequent sample of adolescents at risk for alcoholism, found this polymorphism was significantly related to increased hazardous drinking in adolescents characterized by early life stress. Clarke and colleagues (2011) interpret their findings by stating that the effects of early life stress in adolescents is moderated by KCNJ6 gene via dopaminergic signal disruptions, which enhances the rewarding effects of alcohol, thus

increasing the potential for alcohol abuse in adulthood. Moreover, stress may further enhance predisposition through the effects of cortisol on GIRK2 levels in the brain. Early life stress may also increase pain vulnerability. Nishizawa and colleagues (2009) found an association between KCNJ6 gene polymorphisms and increased demand for pain relief among individuals recovering from major abdominal surgery.

2.1 Genetic Variation Mediates Pharmacological Treatment Effects

There have been genotype effects that increased or decreased the effectiveness of the treatment drugs Naltrexone, Acamprosate, Tiapride, and Bromocriptine. Naltrexone, an opiate antagonist, is one of the most used drugs for treating alcohol addiction. Its highest affinity is for the μ-opioid receptor gene OPRM1. Subjects with the G allele responded the most positively to this treatment, as did those with the T allele of the GABA receptor gene GABRA6. With the GABA receptor, Acamprosate had better results with C allele subjects. Nalmefene is another opioid receptor antagonist that is used to help treat alcohol addiction, though it is not as effective as naltrexone for individuals with the polymorphisms of OPRM1. Nalmefene has not been found to be affected by genotype. Tiapride effectiveness is reduced for A/A genotypes of the DRD2 gene, while Bromocriptine effectiveness is enhanced in subjects with at least one A1 allele of the Taq1A polymorphism, found in the ANKK1 gene (Sturgess, George, Kennedy, Heinz, & Muller, 2011).

3. Genetic Variation & Neural Mechanisms

Dopaminergic circuitry, sensitive to stress in both human and non-human animals, may operate differently in individuals susceptible to psychiatric illnesses including addiction (Mickey et al., 2012). The role of disordered dopaminergic projections from the midbrain to the striatum is recognized in addiction (Mickey et al., 2012). Mickey and colleagues (2012) investigated striatal dopamine release and genetic variation of the serotonin 2C receptor, implicated in neuropsychiatric disorders, in humans subjected to moderate deep muscular pain. DNA was extracted and genotyped using blood collected from participants, which was used to categorized participants as Ser23 carriers and non-carriers. They hypothesized that individuals carrying the Ser23 variant of the serotonin receptor gene (HTR2C) would display greater sensitivity in dopaminergic circuitry as indexed by positron emission tomography (PET) and quantifying D2/D3 radiotracer receptor, binding before and after a validated pain challenge.

Mickey and colleagues (2012) found that Ser23 carriers exhibited greater dopamine release in the putamen, caudate nucleus, and nucleus accumbens, demonstrating that the Ser23 allele of the human serotonin receptor gene (HTR2C) is related to greater striatal dopamine release during the experience of pain in healthy individuals. Moreover, HTR2C Ser23 allele genotype accounted for 12% of the variance of dopamine release. Interestingly, Mickey and colleagues (2012) further explored whether the relationship between the serotonin receptor gene and release of dopamine was explained by differences in pain sensitivity, and found that after adding pain sensitivity and pain score as covariates, the pain by Ser23 interaction persisted in the

nucleus accumbens, but was weakened in the putamen and caudate. Mickey and colleagues (2012) interpret their finding of increased stress-provoked dopamine release among Ser23 carriers by proposing that greater mesoaccumbal stress reactivity may increase the risk of psychiatric disorders among these individuals. The findings of Ebstein and colleagues (1997) lend partial support to this proposal as they found Ser23 carriers displayed reduced traits of reward dependence and persistence, which are implicated in addiction.

Chapter Four:

Conclusion

Pain sensitivity is affected by the interaction of biological, sociocultural, and psychological factors. Pain sensitivity plays an important role in alcohol dependence as the analgesic and hyperalgesic effects of alcohol influence the course of addiction and may significantly influence relapse. Alcohol dependence is a chronically relapsing disorder, with individuals showcasing tremendous difficulty to remain abstinent despite availability of pharmacological and community treatments. While alcohol can initially provide pain reduction, continuing alcohol use leads to reduction in pain tolerance. Moreover, individuals who continue to consume alcohol to manage pain have a worsened prognosis. Thus, while pre-existing alcohol addiction is a possible risk factor for increased pain, pain sensitivity may play a significant role in the development or continuation of alcohol dependence, and longitudinal prospective studies are necessary to shed light on the direction of causality between pain and alcoholism (Turk, 1997). The link between pain and alcohol addiction is further supported in that the neural circuitry that mediates pain response is also implicated in addiction processes. This literature review demonstrates strong support for the existence of a link between pain sensitivity and alcohol dependence.

Directions for Future Research

While the studies reviewed have demonstrated that there exists a potential link between pain sensitivity and addiction potential, future studies should investigate the

causal direction of such a link. For instance, does heightened pain sensitivity lead to addiction? Conversely, are individuals who are less sensitive to pain protected from developing addiction? Delving into these questions in empirical research can offer groundbreaking insights into the interminable hold of alcohol addiction. Beneficial studies may include examining adolescents' pain sensitivity to stimuli presented during functional magnetic resonance (fMRI) scanning and seeing if pain sensitivity is indexed by genetic factors or a family history of alcoholism. Moreover, it would be fascinating to determine if pain sensitivity can be altered by treatment with neurofeedback or meditation training, and if such treatment would buffer those at risk for alcoholism from developing alcoholism. A recent fMRI study by Zeidan and colleagues (2011) showed significant reductions in ratings of pain intensity and unpleasantness in individuals who underwent meditation training. The hope would be that this type of preventative treatment may protect those at risk from developing alcohol dependence.

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